

chimeric hybrid conjugate molecules, designed to contain an opioid analgesic moiety or principle capable of engendering opioid-dependent analgesia without opioid tolerance development, possesses well established, clinically-efficacious, pharmacological properties for acute and chronic pain relief that are operationally defined by those of the prototype opioid alkaloid morphine. As such, a general class of chimeric hybrid conjugate molecules capable of engendering efficacious, morphine-like, opioid-dependent analgesia for a variety of clinically defined pain indications without tolerance development is novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention is not predictable according to the teachings of Rothman [1, Rothman, R.B. (1992) A review of the role of anti-opioid peptides in morphine tolerance and dependence. *Synapse* 12, 129-138.] who has formulated models and mechanisms of morphine and opioid tolerance and dependence that are exclusively mediated by functional changes in receptors and peptide transmitter systems within the CNS. Notably, Rothman teaches that adaptive mechanisms of morphine tolerance and dependence involve CNS neuropeptide systems that normally mediate homeostatic responses to attenuate adverse physiological effects of prolonged morphine exposure. The present invention is a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without opioid tolerance development that is functionally dependent on simultaneous activation of mu opioid and substance P receptors within the CNS following parenteral administration outside the CNS morphine and, as such, its pharmacological effects are intrinsically a function of this class of molecules to permeate the mammalian blood brain barrier (BBB) as an intact chemical entity. Accordingly, the analgesic and anti-opioid tolerance properties of this general class of chimeric hybrid conjugate molecules are functionally linked to chemical and pharmacological integrity of each of the receptor activating domains to effectively permeate the BBB within a capped covalently bonded linear sequence. According to the teachings of Rothman, it is not intuitively obvious and predictable that molecules of the general class of chimeric hybrid conjugate molecules possessing an opioid analgesic moiety or principle capable of engendering clinically-efficacious, opioid-dependent, acute and chronic pain relief equivalent to that produced by the prototype opioid alkaloid morphine will activate homeostatic anti-tolerance mechanisms within the CNS. As such, the requirement for an intact chimeric hybrid conjugate molecule to permeate the mammalian BBB as an intact chemical entity to enable each of its mu opioid and substance P receptor activation domains to effect clinically efficacious opioid analgesia without tolerance development distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention is not predictable according to the teachings of Foran and coworkers [2, Foran, S.E., Carr, D.B., Lipkowski, A.W., Maszczyńska, I., Marchand, J.E., Misicka, A., Beinborn, M., Kopin, A.S., & Kream, R.M. (2000) A substance P-opioid chimeric peptide as a novel non-tolerance forming analgesic, *Proc. Natl. Acad. Sci. USA* 97, 7621-7626] in reference to those of Rothman. Foran and coworkers teach that repeated administration of a chimeric peptide containing mu opioid and substance P receptor activating domains into the rat CNS produces opioid-dependent

analgesia without tolerance development that is functionally linked to its SPR activating domain. Because the present invention is a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without opioid tolerance development that is functionally dependent on simultaneous activation of mu opioid and substance P receptors within the CNS following parenteral administration outside the CNS, its pharmacological effects are intrinsically a function of this class of molecules to permeate the mammalian BBB as an intact chemical entity. As such, the requirement for an intact chimeric hybrid conjugate molecule to permeate the mammalian BBB as an intact chemical entity to enable each of its mu opioid and substance P receptor activation domains to effect clinically efficacious opioid analgesia without tolerance development is not predictable by the teachings of Foran and coworkers in reference to those of Rothman and distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention is not predictable according to the teachings of Nyberg and coworkers [3, Zhou, Q., Karlsson, K., Liu, Z., Johansson, P., Le Greves, M., Kiuru, A. & Nyberg, F. (2001) Substance P endopeptidase-like activity is altered in various regions of the rat central nervous system during morphine tolerance and withdrawal. *Neuropharmacology* 41, 246-253.] in reference to the teachings of Foran and coworkers and Rothman. Nyberg and coworkers teach that CNS metabolism of SP and SPR activating domains via SP-specific endopeptidase activity is altered following morphine tolerance development and significant increases in SP-specific endopeptidase activity may be responsible for compensatory physiological responses in opioid tolerant animals. Because the present invention is a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without opioid tolerance development that is functionally dependent on simultaneous activation of mu opioid and substance P receptors within the CNS following parenteral administration outside the CNS, its pharmacological effects are intrinsically a function of this class of molecules to permeate the mammalian BBB as an intact chemical entity. As such, the requirement for an intact chimeric hybrid conjugate molecule to permeate the mammalian BBB as an intact chemical entity to enable each of its mu opioid and substance P receptor activation domains to effect clinically efficacious opioid analgesia without tolerance development without altering compensatory SP-metabolizing systems is not predictable by the teachings of Nyberg and coworkers in reference to those of Foran and coworkers and Rothman and distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention as a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without tolerance development that is functionally dependent on BBB transport is not predictable according to the teachings of Syvanen and coworkers (4) who studied influx and efflux processes of morphine and morphine-glucuronides in relation to their BBB permeability properties and brain concentrations. Syvanen and coworkers teach that efficacious BBB permeation is determined by a combination of influx hindrance (a gatekeeper function in the luminal membrane that is functionally linked to P-glycoprotein activation) and efflux enhancement by transporters that pick up molecules on one side of the luminal or

abluminal membrane and release them on the other side. The production of opioid-dependent analgesia for acute and chronic pain indications via a facilitative method of BBB transport of morphine and morphine congeners by covalently bonded heterologous substance P receptor activating domains as found in the structure of chimeric hybrid conjugate molecules is not predictable by the general principle of BBB permeation by morphine and morphine congeners codified by Syvanen and coworkers. Conversely, the production of opioid-dependent analgesia for acute and chronic pain indications via a facilitative method of BBB transport of substance P fragments or non-peptide substance P receptor activating domains by covalently bonded heterologous morphine, morphine congeners, and opioid peptide mu opioid receptor activating domains as found in the structure of chimeric hybrid conjugate molecules is not predictable by the teachings of Syvanen and coworkers.

In light of the work of Syvanen and coworkers cited above, the teachings of Liederer and coworkers (5) provide us with guidelines by which to construct a general class of chimeric hybrid conjugate molecules capable of opioid-dependent analgesia for acute and chronic pain indications that combine any non-peptide opioid with any active fragment of substance P, or any peptide, for transport across the BBB. Liederer and coworkers teach that low BBB permeation is functionally linked to strong substrate activity for P-glycoprotein and efflux transporters in this biological barrier that is markedly enhanced for a variety of tested opioid peptide analogs sharing a common covalent cyclical structure. In contrast, capped, electrically neutral, linear derivatives of a variety of opioid peptide analogs with acetylation of the N-terminal and amidation of the C-terminal ends display efficacious permeation of the BBB via low substrate activity for P-glycoprotein and efflux transporters in this biological barrier.

Application of guidelines derived from the teachings of Liederer and coworkers in reference to the teachings of Syvanen and coworkers will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules capable of producing opioid-dependent analgesia for acute and chronic pain indications without tolerance development via simultaneous activation of mu opioid and substance P receptors within the CNS. Chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of substance P, or any peptide, for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with the non-peptide opioid covalently bonded to the N-terminal end of the substance P fragment through a 4-6 carbon molecular linker and containing a neutral amide group at the C-terminal end of the substance P fragment. Chimeric hybrid conjugate molecules that combine any opioid peptide, or for that matter any peptide, with any non-peptide substance P receptor activating domain for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with acetylation of the N-terminal of the opioid peptide that is covalently bonded at the C-terminal end to the non-peptide substance P receptor activating domain through a 4-6 carbon molecular linker. Finally, the teachings of

Schiller (6) in reference to those of Syvanen and coworkers (4) and Liederer and coworkers (5) demonstrate a permissive chemical heterocyclic substitution in the internal domains of capped linear opioid peptide sequences that allow for efficacious BBB permeation, thereby providing validation for my specification indicating d-glucuronic acid, as a representative example of a closed-ring carbon structure, as an appropriate 6 carbon linker connecting linear mu opioid and substance P receptor activating domains within chimeric hybrid conjugate molecules.

The production of opioid-dependent analgesia for acute and chronic pain indications via a facilitative method of BBB transport of morphine and morphine congeners by covalently bonded heterologous substance P receptor activating domains or conversely, of BBB transport of substance P fragments or non-peptide substance P receptor activating domains by covalently bonded heterologous morphine, morphine congeners, and opioid peptide mu opioid receptor activating domains, requires maintenance of opioid and substance P activities in chemically-modified structures of chimeric hybrid conjugate molecules. The teachings of Portoghese and coworkers (7,8) in reference to those of Liederer and coworkers and Schiller provide specific indications for maintaining opioid activity following chemical modification of the multi-ringed non-peptide structures characteristic of morphinans, benzomorphans, and phenylpiperidines, as described for opioid peptide analogs. The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

In brief, the teachings of Portoghese and coworkers provide the following guidelines for preserving high affinity mu opioid receptor activity for all non-peptide opioid domains found in the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS. Their teachings indicate that the A ring OH group at position 3 must be conserved during synthesis and/or conjugation to active substance P fragments through a linker molecule. Consistent with the major body of published opioid research, conservation of the A ring OH group at position 3 is required for high affinity mu opioid receptor activation. Thus, the A ring OH group at position 3 may be protected during synthesis or conjugation via covalent linkage to well recognized blocking groups that include Acetyl or T-butyl moieties. Following synthesis or construction of chimeric hybrid conjugates the Acetyl or T-butyl moieties are removed by gentle chemical treatment yielding non-peptide chemical moieties with a free A ring OH group at position 3.

The teachings of Portoghese and coworkers also indicate that the B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan

multi-ringed structure is an appropriate site for chemical modification due to its location at a point distal to the obligate A ring OH group at position 3 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure. Chemical modification and linkage of the non-peptide opioid domain of molecules of the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS at a position spatially separated and distal to the obligate A ring OH group will permit binding in a sterically unhindered fashion to the mu opioid receptor. The B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure may be further oxidized to a keto group with full retention of opioid activity. OH and keto groups are generally employed as chemical moieties capable of covalently linking discrete chemical entities through ester or ether chemistry. Finally, the teachings of Portoghese and coworkers indicate that multiple positions of the B ring, including the OH group at position 6 of morphine, or an equivalent position on the morphinan or benzomorphan multi-ringed structure, may be chemically modified without effecting opioid activity mediated by the obligate A ring OH group.

The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

The teachings of Cascieri and Liang (9) and Mantyh and coworkers (10) provide specific indications for maintaining SP activity for C-terminal fragments of SP within a general class of chimeric hybrid conjugate molecules capable of producing opioid-dependent analgesia for acute and chronic pain indications without tolerance development via simultaneous activation of mu opioid and substance P receptors within the CNS. The rules provided by Cascieri and Liang and Mantyh and coworkers are considered to be general rules for evaluating bioactivities of fragments of SP by established investigators in SP research. According to their teachings and consistent with generally accepted formulations, all fragments of SP maintaining a fully intact C-terminal peptide domain equal to or greater than 5 amino acids have been determined to possess biological activity using a variety of testing paradigms. In the present invention, biologically active fragments of SP include SP 3-11, SP 4-11, SP 5-11, SP 6-11, and SP 7-11. All biologically active SP fragments contain only one free alpha amino group that is located at a site distal to SPR recognition domain and is utilized as the point of linkage of all active fragments of SP within the structure of the class of chimeric hybrid molecules described in the present invention. In sum, the teachings of Cascieri and Liang and Mantyh and coworkers in reference to the teachings of Portoghese and coworkers, Liederer and coworkers, and Schiller provide guidelines that will enable any person skilled in the art to which it pertains to make and use the invention commensurate in

scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

A. Chimeric hybrid conjugate molecules that combine *any non-peptide opioid with any active fragment of SP, or any peptide, for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB* are constructed as capped, electrically neutral, linear sequences with the non-peptide opioid covalently bonded to the N-terminal end of the substance P fragment through a 4-6 carbon molecular linker, or according to the teachings of Schiller a more complex heterocyclic structure, and containing a neutral amide group at the C-terminal end of the SP fragment. Figure 1 depicts the construct of a linear chemical structure within the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS that contains a representative member of the morphinan, benzomorphan, or phenylpiperidine classes of non-peptide opioid alkaloid in covalent linkage to a representative member of the class of 4-6 carbon or more complex heterocyclic molecular linker in covalent linkage to a representative member of the class of biologically active fragments of SP that include SP 3-11, SP 4-11, SP 5-11, SP 6-11, and SP 7-11, and their chemically modified congeners.

Figure 1: Construct of a chimeric hybrid conjugate molecule that combines any non-peptide opioid with any active fragment of SP

Non-peptide opioid alkaloid	Molecular linker	Active fragment of substance P
-----------------------------	------------------	--------------------------------

Representative candidate molecules chosen from the morphinan, benzomorphan, or phenylpiperidine classes of non-peptide opioid alkaloids, 4-6 carbon or more complex heterocyclic molecular linkers, and biologically active fragments of SP are listed in Table 1 and one of each may be covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules according to guidelines gleaned from the teachings of Portoghese and coworkers (7,8), Cascieri and Liang (9) and Mantyh and coworkers (10) in reference to those of Liederer and coworkers (5) and Schiller (6).

Table 1: Representative molecules covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of SP to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB.

Non-peptide opioid alkaloids	Molecular linkers	Active fragments of substance P
Morphine	Succinic acid	substance P 3-11

Dihydromorphine	Gamma hydroxybutyric acid	substance P 4-11
Oxymorphone	d-glucuronic acid	substance P 5-11
Oxycodone	l-glucuronic acid	substance P 6-11
Hydrocodone	oxaloacetic acid	substance P 7-11
Pentazocine	alpha ketoglutaric acid	D-nor-leu substance P 3-11
Cyclazocine	inositol	D-nor-leu substance P 4-11
Fentanyl	tetrahydroisoquinoline-3-carboxylic acid	D-nor-leu, D-tryp substance P 3-11
Sufentanyl		D-nor-leu, D-tryp substance P 4-11

B. Chimeric hybrid conjugate molecules that combine any *mu* opioid receptor-prefering opioid peptide, or for that matter any peptide, with any non-peptide SPR activating domain for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with acetylation of the N-terminal of the opioid peptide that is covalently bonded at the C-terminal end to the non-peptide SPR activating domain through a 4-6 carbon molecular linker, or according to the teachings of Schiller (6) a more complex heterocyclic structure. Figure 2 depicts the construct of a linear chemical structure within the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS that contains a representative member of the class of MOR-prefering opioid peptide in covalent linkage to a representative member of the class of 4-6 carbon or more complex heterocyclic molecular linker in covalent linkage to a representative member of the class of non-peptide SPR activating domain.

Figure 2: Construct of a chimeric hybrid conjugate molecule that combines any MOR-prefering opioid peptide with any non-peptide SPR activating domain.

Mu opioid receptor-prefering opioid peptide	Molecular linker	Non-peptide substance P receptor activating domain
---	------------------	--

Representative candidate molecules chosen from the class of MOR-prefering opioid peptides, 4-6 carbon or more complex heterocyclic molecular linkers, and non-peptide SPR activating molecules are listed in Table 2 and one of each may be covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules according to guidelines gleaned from the teachings of Portoghese and coworkers (7,8), Cascieri and Liang (9) and Mantyh and coworkers (10) in reference to those of Liederer and coworkers (5) and Schiller (6).

Table 2: Representative molecules covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules that combine any MOR-prefering opioid peptide with any non-peptide SPR activating domain for production of opioid-dependent

analgesia for acute and chronic pain indications without tolerance development via transport across the BBB.

Mu opioid receptor-preferring opioid peptides	Molecular linkers	Non-peptide substance P receptor activating molecules
N-acetyl methionine enkephalin N-acetyl methionine enkephalin-Arg-Phe N-acetyl, D-ala2, methionine enkephalin N-acetyl leucine enkephalin N-acetyl leucine enkephalin-Arg-Gly-Leu N-acetyl,D-ala2, leucine enkephalin N-acetyl dynorphin A (1-13) N-acetyl endomorphin 2	Succinic acid Gamma hydroxybutyric acid d-glucuronic acid l-glucuronic acid oxaloacetic acid alpha ketoglutaric acid inositol tetrahydroisoquinoline-3-carboxylic acid	L-733,061 (partial agonist) GR7362 RP67580 (partial agonist)

The Specification is amended as per the attached amended Specification.

The Drawings are amended as per the attached amended Drawings.

The Sequence Listing is amended as per the attached amended Sequence Listing.

Further Response to Paragraph 6

A. Further defined in parts 5, 5 [sic] and 6, above.

B. Further defined in parts 5, 5 [sic] and 6, above.

C. I claim that the intrinsic chemical/pharmacological actions of hybrid chimeric molecules produce opioid analgesia without opioid tolerance development and hybrid chimeric molecules act as adjuvants to traditional opioid analgesics by functionally inhibiting tolerance mediated by these compounds.

D. Further defined in parts 5, 5 [sic] and 6, above.

Response to Paragraph 7

I respectfully submit that my response to paragraphs 5, 5 [sic] and 6 provides sufficient rationale to overturn double patenting rejections provided by 6,881,829 and 6,759, 520.

Response to Paragraph 8

I respectfully submit that my response to paragraphs 5, 5 [sic] and 6 provides sufficient rationale to overturn prior art rejections provided by 6,759, 520.

Response to Paragraph 9

Claim 1 is novel and unpredictable by the teachings of Wainer and coworkers. Wainer and coworkers teach that morphine is covalently linked to BSA via a succinyl bond at position 3. The procedure of Wainer and coworkers is a method for generating antibodies to morphine via conjugation to a large protein BSA that by its chemical nature does not cross the BBB. Antibody production is generally believed to be functionally linked to processing of antigen or hapten linked to carrier protein in the blood. By definition, antisera contain antibody molecules generated by white blood cell processes in the peripheral circulation. Accordingly, Wainer and coworkers teach that conjugation of morphine to BSA effectively represents a peripheral blood pool of conjugated morphine that is never meant to cross the BBB. Furthermore, as discussed in our rebuttal to points 4 and 5 above, the teachings of Wainer and coworkers link morphine to BSA through the A ring OH group at position 3, thereby inactivating the opioid receptor binding activity of morphine. The teachings of Wainer and coworkers are therefore not functionally linked to prior observations of Foran and coworkers and do not provide unpatentable criteria by which to reject Claims 1.

Materials Cited Above


1. Rothman, R.B. (1992) A review of the role of anti-opioid peptides in morphine tolerance and dependence. *Synapse* 12, 129-138.
2. Foran, S.E., Carr, D.B., Lipkowski, A.W., Maszczynska, I., Marchand, J.E., Misicka, A., Beinborn, M., Kopin, A.S., & Kream, R.M. (2000) A substance P-opioid chimeric peptide as a novel non-tolerance forming analgesic, *Proc. Natl. Acad. Sci. USA* 97, 7621-7626.
3. Zhou, Q., Karlsson, K., Liu, Z., Johansson, P., Le Greves, M., Kiuru, A. & Nyberg, F. (2001) Substance P endopeptidase-like activity is altered in various regions of the rat central nervous system during morphine tolerance and withdrawal. *Neuropharmacology* 41, 246-253.
4. Syvanen, S., Xie, R., Sahin, S. & Hammarlund-Udenaes, M. (2006) Pharmacokinetic consequences of active drug efflux at the blood-brain barrier. *Pharm. Res.* 23, 705-717.
5. Liederer, B.M., Fuchs, J., Vander Velde, D., Siahaan, T.J. & Borchardt, R.T. (2006) Effects of amino acid chirality and the chemical linker on the cell permeation characteristics of cyclic prodrugs of opioid peptides. *J Med Chem.* 49, 1261-1270.
6. Schiller, P.W. (2005) Opioid peptide-derived analgesics. *A.A.P.S. J.* 7, E560-567.
7. Bolognesi, M.L., Ojala, W.H., Gleason, W.B., Griffin, J.F., Farouz-Grant, F., Larson, D.L., Takemori, A.E. & Portoghese, P.S. (1996) Opioid antagonist

activity of naltrexone-derived bivalent ligands: importance of a properly oriented molecular scaffold to guide "address" recognition at kappa opioid receptors. J. Med. Chem. 39, 1816-1822.

8. Portoghese, P.S. (2001) From models to molecules: opioid receptor dimers, bivalent ligands, and selective opioid receptor probes. J. Med. Chem. 44:2259-69.
9. Cascieri, M.A & Liang, T. (1983) Characterization of the substance P receptor in rat brain cortex membranes and the inhibition of radioligand binding by guanine nucleotides. J Biol. Chem. 258, 5158-5164.
10. Mantyh, P.W., Gates, T., Mantyh, C.R. & Maggio, J.E. (1989) Autoradiographic localization and characterization of tachykinin receptor binding sites in the rat brain and peripheral tissues. J. Neurosci. 9, 258-279.26.

Respectfully yours,

Attachments
Amendment No. 1 to Claims
Amended Specification
Amended Drawings
Amended Sequence Listing



Richard M. Kream, Ph.D.
% Chimeracom, LLC
Wall Street Plaza, 23rd Floor
New York, NY 10005-1875
Tel: 631-549-2064; Fax: 212-344-4294

Certificate of Faxing

I certify that this correspondence is being filed by fax to ~~703-872-9306~~ ⁵⁷¹⁻²⁷³⁻⁸³⁰⁰ on the date

below.

Date: May 15, 2006


Richard M. Kream, Ph.D.
Applicant

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.